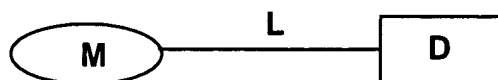


**AMENDMENTS TO THE CLAIMS**

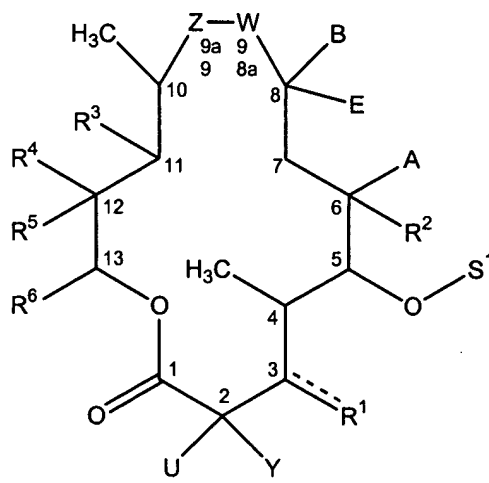
1. (Currently Amended) A compound of Formula I:



**I**

wherein

~~M represents a macrolide subunit~~ M represents a group of  
Formula II:



**II**

wherein:

Z and W independently are: >C=O, >CH<sub>2</sub>, >CH-NR<sub>t</sub>R<sub>s</sub>, >N-R<sub>N</sub> or >C=N-R<sub>M</sub> or a bond

wherein:

R<sub>t</sub> and R<sub>s</sub> independently are hydrogen or alkyl;

R<sub>M</sub> is hydroxy, alkoxy, substituted alkoxy or OR<sup>p</sup>;

R<sub>N</sub> is hydrogen, R<sup>p</sup>, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, or -C(X)-NR<sub>i</sub>R<sub>s</sub>; wherein X is =O or =S;

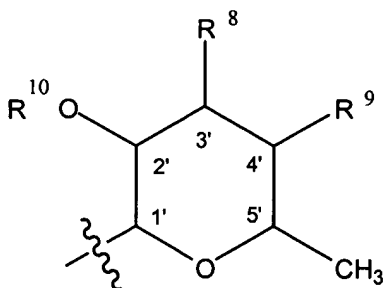
provided that Z and W cannot both simultaneously be,  $>\text{C}=\text{O}$ ,  $>\text{CH}_2$ ,

$$\underline{>\text{CH-NR}_t\text{R}_s, >\text{N-R}_N \text{ or } >\text{C=N-R}_M \text{ or a bond,}}$$

U and Y independently are hydrogen, halogen, alkyl, or hydroxyalkyl;

$R^1$  is hydroxy,  $OR^p$ ,  $-O-S^2$  group or an  $=O$ ;

S<sup>1</sup> is a sugar moiety of formula:



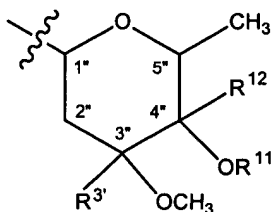
wherein

R<sup>8</sup> and R<sup>9</sup> are both hydrogen or together form a bond, or R<sup>9</sup> is hydrogen and R<sup>8</sup> is -N(CH<sub>3</sub>)R<sup>y</sup>, wherein

R<sup>y</sup> is R<sup>p</sup>, R<sup>z</sup> or -C(O)R<sup>z</sup> wherein R<sup>z</sup> is hydrogen or alkyl or alkenyl or alkynyl or cycloalkyl or aryl or heteroaryl or alkyl substituted with C<sub>2</sub>-C<sub>7</sub>-alkyl, C<sub>2</sub>-C<sub>7</sub>-alkenyl, C<sub>2</sub>-C<sub>7</sub>-alkynyl, aryl or heteroaryl

$R^{10}$  is hydrogen or  $R^p$ ;

S<sup>2</sup> is a sugar moiety of formula :



wherein:

R<sup>3</sup>' is hydrogen or methyl;

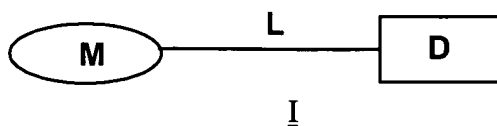


bucloxic acid, butibufen, carprofen, celexocib, chromoglycate, cinmetacin, clindanac, clopirac, sodium diclofenac, diflunisal, ditazol, droxicam, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenac, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glutametacin, glycol salicylate, ibufenac, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, montelukast, nabumetone, naproxen, niflumic acid, nimesulide, olsalazine, oxaceprol, oxaprozin, oxyphenbutazone, paracetamol, parsalmide, perisoxal, phenyl-acethyl-salicylate, phenylbutazone, phenylsalicylate, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, reserveratol, salacetamide, salicylamide, salicylamide-O-acetyl acid, salicylsulphuric acid, salicin, salicylamide, salsalate, sulindac, suprofen, suxibutazone, tamoxifen, tenoxicam, tiaprofenic acid, tiaramide, ticlopridine, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol, zafirlukast and cyclosporin;

L is a linker molecule to which each of M and D are covalently linked; and

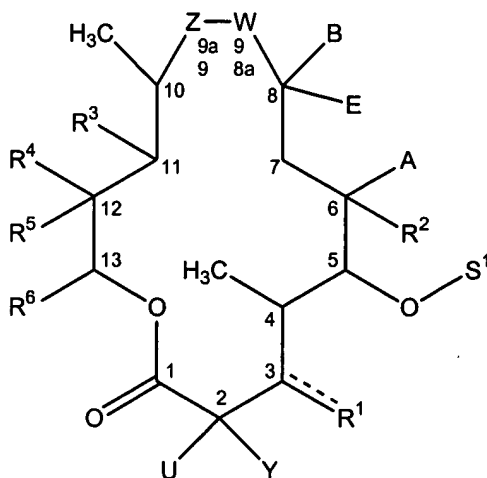
pharmaceutically acceptable salts and solvates thereof and individual diastereoisomers thereof.

2. (Currently Amended) A compound ~~according to claim 1~~ of the Formula I



wherein M represents a group of

Formula II:



## II

wherein:

Z and W independently are:  $>C=O$ ,  $>CH_2$ ,  $>CH-NR_tR_s$ ,  $>N-R_N$  or  $>C=N-R_M$  or a bond

wherein:

$R_t$  and  $R_s$  independently are hydrogen or alkyl;

$R_M$  is hydroxy, alkoxy, substituted alkoxy or  $OR^p$ ;

R<sub>N</sub> is hydrogen, R<sup>p</sup>, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, or -C(X)-NR<sub>t</sub>R<sub>s</sub>; wherein X is =O or =S;

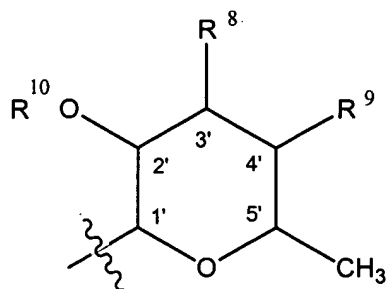
provided that Z and W cannot both simultaneously be,  $>\text{C}=\text{O}$ ,  $>\text{CH}_2$ ,

$$>\text{CH}-\text{NR}_t\text{R}_s, >\text{N}-\text{R}_N \text{ or } >\text{C}=\text{N}-\text{R}_M \text{ or a bond,}$$

U and Y independently are hydrogen, halogen, alkyl, or hydroxyalkyl;

R<sup>1</sup> is hydroxy, OR<sup>p</sup>, -O-S<sup>2</sup> group or an =O;

S<sup>1</sup> is a sugar moiety of formula:



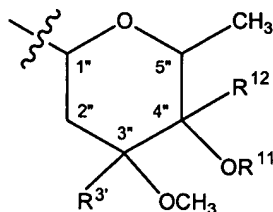
wherein

$R^8$  and  $R^9$  are both hydrogen or together form a bond, or  $R^9$  is hydrogen and  $R^8$  is -  
 $N(CH_3)R^y$ , wherein

$R^y$  is  $R^p$ ,  $R^z$  or  $-C(O)R^z$  wherein  $R^z$  is hydrogen or alkyl or alkenyl or alkynyl or  
 cycloalkyl or aryl or heteroaryl or alkyl substituted with  $C_2$ - $C_7$ -alkyl,  $C_2$ - $C_7$ -  
 alkenyl,  $C_2$ - $C_7$ -alkynyl, aryl or heteroaryl

$R^{10}$  is hydrogen or  $R^p$ ;

$S^2$  is a sugar moiety of formula :



wherein:

$R^{3'}$  is hydrogen or methyl;

$R^{11}$  is hydrogen,  $R^p$  or  $O-R^{11}$  is a group that with  $R^{12}$  and with C/4" carbon atom forms a  
 $>C=O$  or epoxy group;

$R^{12}$  is hydrogen or a group that with  $O-R^{11}$  group and with C/4" carbon atom forms a  
 $>C=O$  or epoxy group;

$R^2$  is hydrogen, hydroxy,  $OR^p$  or alkoxy

A is hydrogen or methyl;

B is methyl or epoxy;

E is hydrogen or halogen;

$R^3$  is hydroxy,  $OR^p$ , alkoxy or  $R^3$  is a group that with  $R^5$  and with C/11 and C/12 carbon  
 atoms forms a cyclic carbonate or carbamate; or if W or Z is  $>N-R_N$   $R^3$  is a group that with W or Z  
 forms a cyclic carbamate;







A and B are methyl;

E is hydrogen;

$R^2$  is hydroxy or methoxy;

S<sup>1</sup> represents desosamine sugar wherein R<sup>8</sup> is selected from: hydrogen, methyl, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino or C<sub>1</sub>-C<sub>6</sub> dialkylamino;

$R^9$  and  $R^{10}$  are hydrogen;

R<sup>1</sup> is hydroxy or the O-S<sup>2</sup> group wherein the S<sup>2</sup> represents a cladinoso sugar wherein:

R<sup>11</sup> is hydrogen, or O-R<sup>11</sup> is a group that with R<sup>12</sup> and with C/4" carbon atom forms a >C=O or epoxy group; R<sup>12</sup> is hydrogen or a group that with O-R<sup>11</sup> and with C/4" carbon atom forms a >C=O or epoxy group;

R<sup>13</sup> is methyl;

U is hydrogen

Y is methyl;

R<sub>6</sub> is hydroxy, methyl or ethyl;

R<sup>5</sup> is hydrogen, hydroxy, methoxy or a group that with R<sup>3</sup> and with C/11 and C/12 carbon atoms forms a cyclic carbonate or carbamate bridge;

R<sup>3</sup> is hydroxy or a group that forms a cyclic carbamate bridge with W or Z, or R<sup>3</sup> is a group that with R<sup>5</sup> and with C/11 and C/12 carbon atoms forms a cyclic carbonate or carbamate bridge;

R<sup>4</sup> is methyl;

provided that the linkage is through the nitrogen of Z at N/9a position or through the carbon of R<sup>12</sup> or through the oxygen of R<sup>11</sup> both at C/4"position of the S<sup>2</sup> sugar.

6. (Currently Amended) A compound according to claim [[3]] 2 wherein

X<sup>1</sup> is -CH<sub>2</sub>- or -OC(O)-;

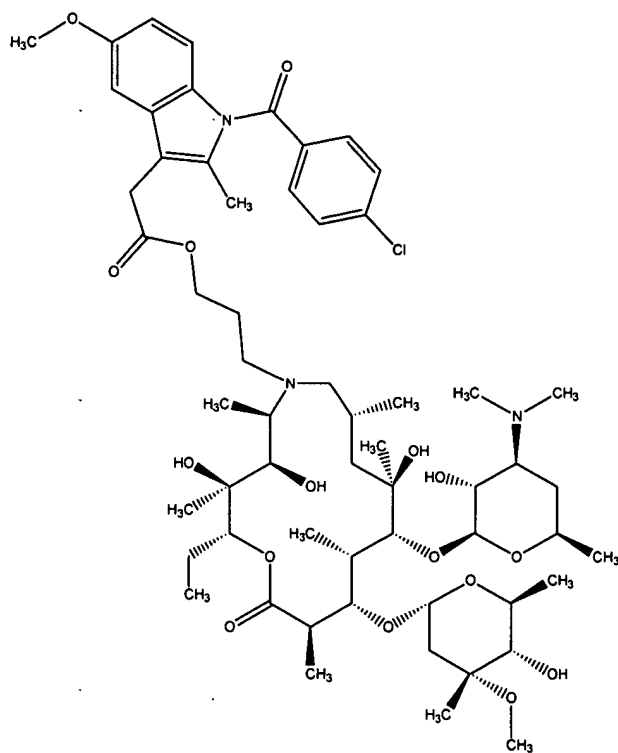
$X^2$  is  $-\text{NHC}(\text{O})-$ ;

Q is -NH- or absent.

7. (Currently Amended) A compound according to claim [[4]] 2 wherein

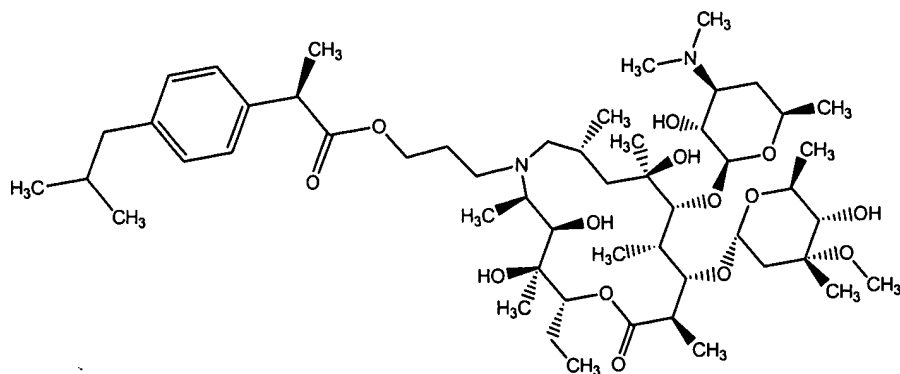
**D** is derived from a NSAID selecting from the group consisting of: S-(+) - ibuprofen, indomethacin, flurbiprofen, naproxen, ketoprofen, acetyl salicylic acid, sulindac, etodolac, ketorolac, suprofen, flunixin, diclofenac sodium and tolmetin sodium.

8. (Currently Amended) A compound of the formula



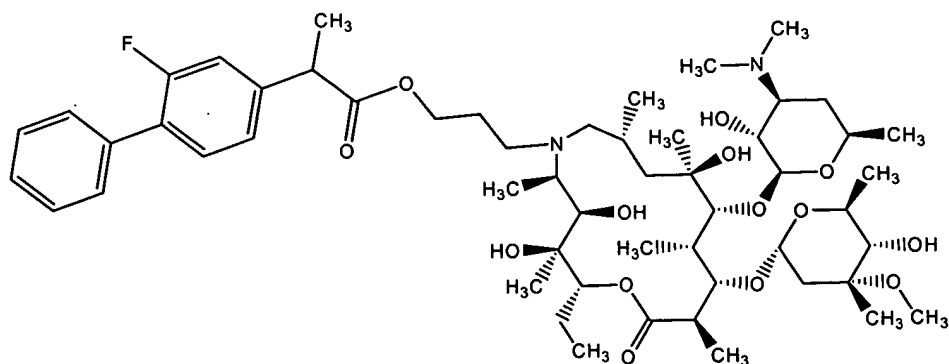
and pharmaceutically acceptable salts and solvates thereof.

9. (Currently Amended) A compound of the formula



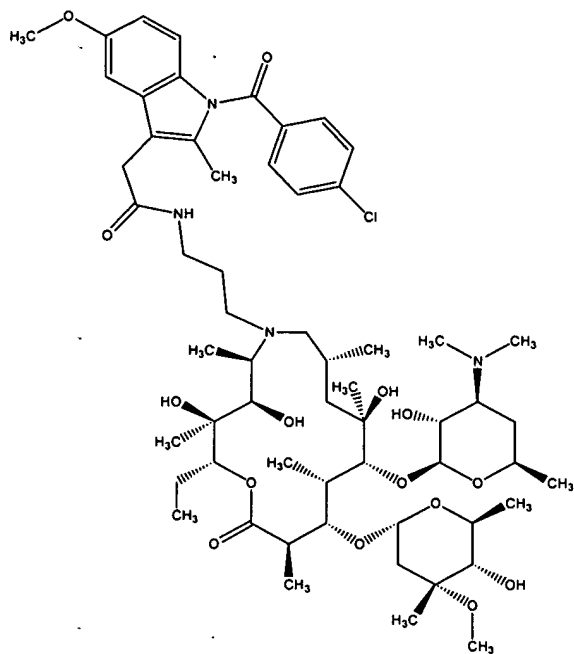
and pharmaceutically acceptable salts and solvates thereof.

10. (Currently Amended) A compound of the formula



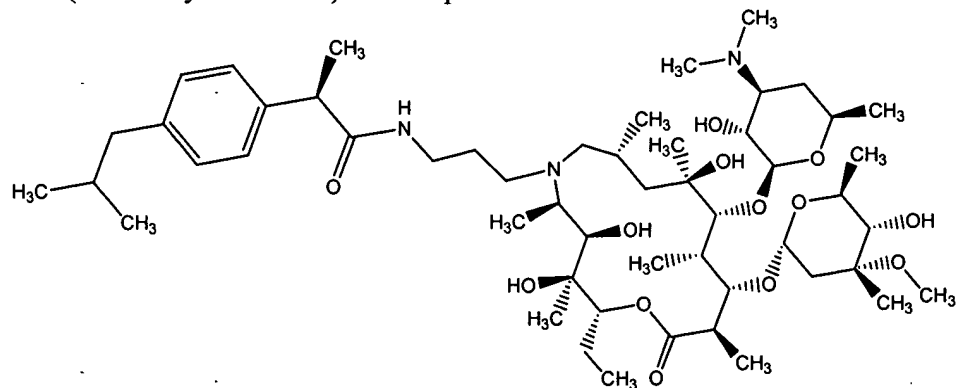
and pharmaceutically acceptable salts and solvates thereof.

11. (Currently Amended) A compound of the formula



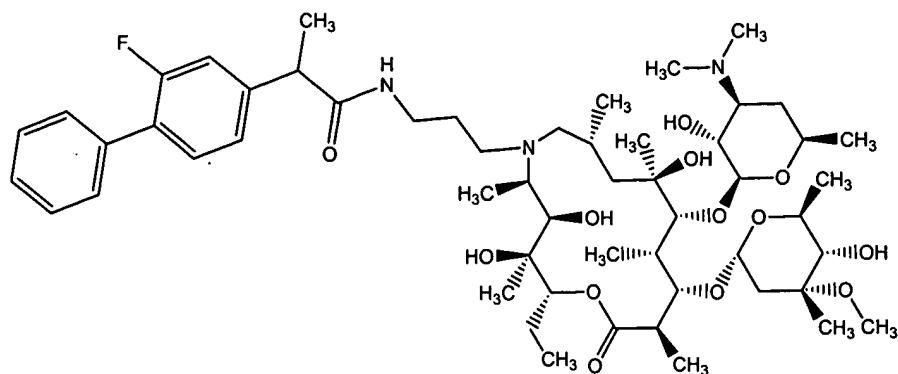
and pharmaceutically acceptable salts and solvates thereof.

12. (Currently Amended) A compound of the formula

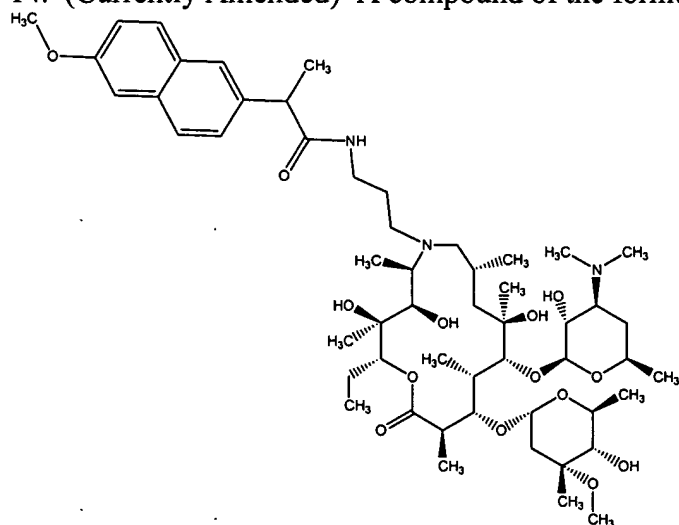


and pharmaceutically acceptable salts and solvates thereof.

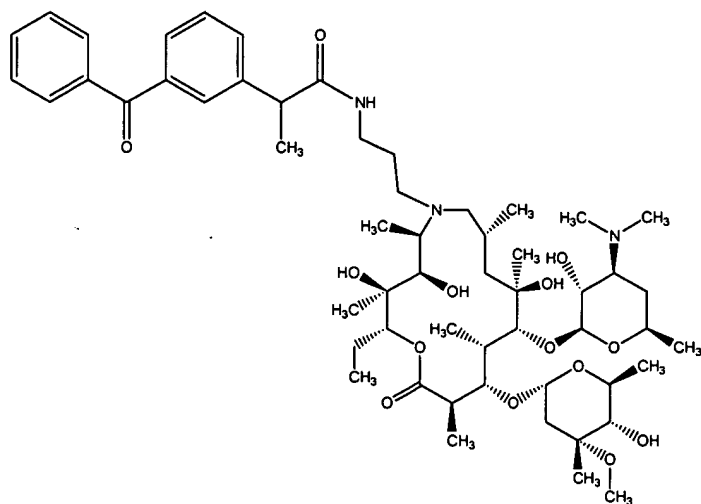
13. (Currently Amended) A compound of the formula



14. (Currently Amended) A compound of the formula

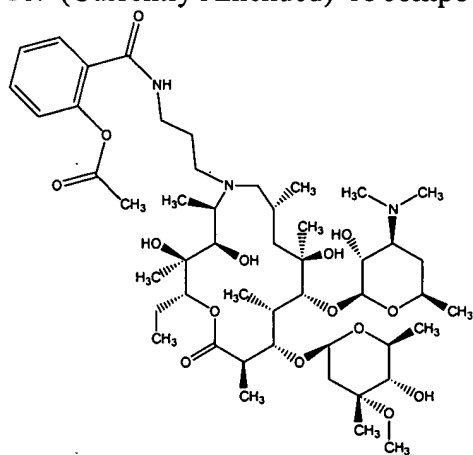


15. (Currently Amended) A compound of the formula



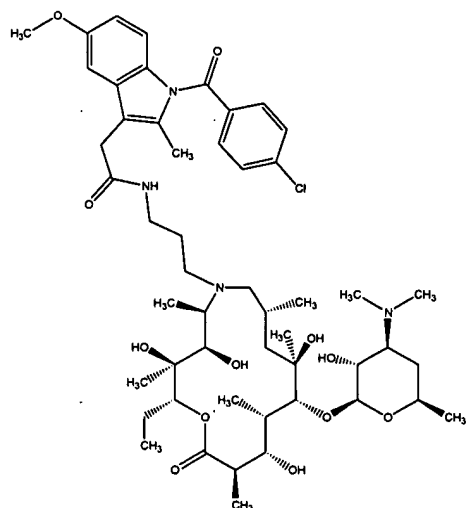
and pharmaceutically acceptable salts and solvates thereof.

16. (Currently Amended) A compound of the formula



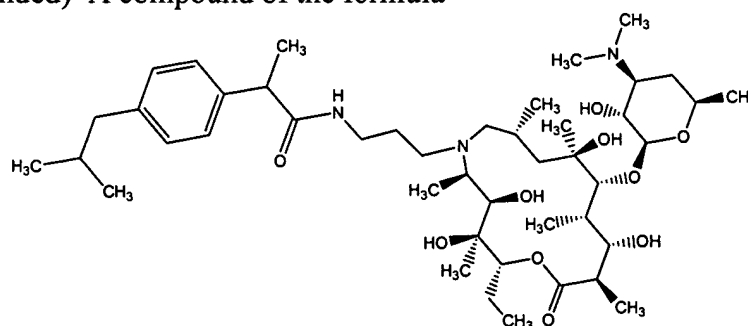
and pharmaceutically acceptable salts and solvates thereof.

17. (Currently Amended) A compound of the formula



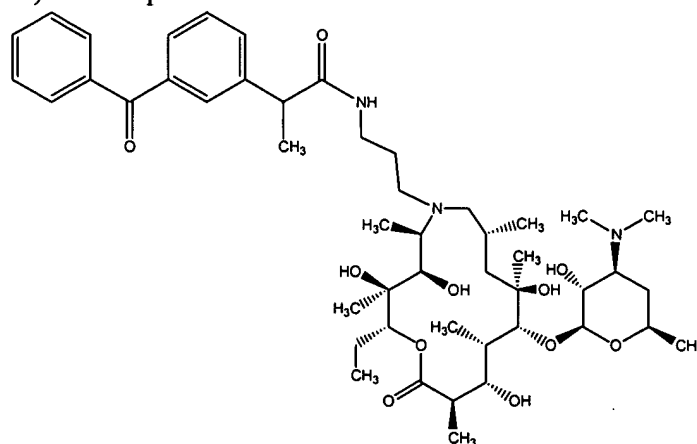
and pharmaceutically acceptable salts and solvates thereof.

18. (Currently Amended) A compound of the formula



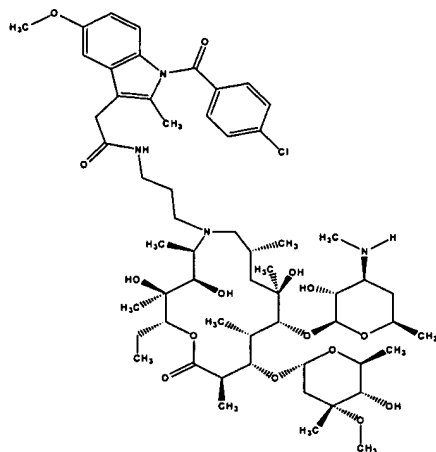
and pharmaceutically acceptable salts and solvates thereof.

19. (Currently Amended) A compound of the formula



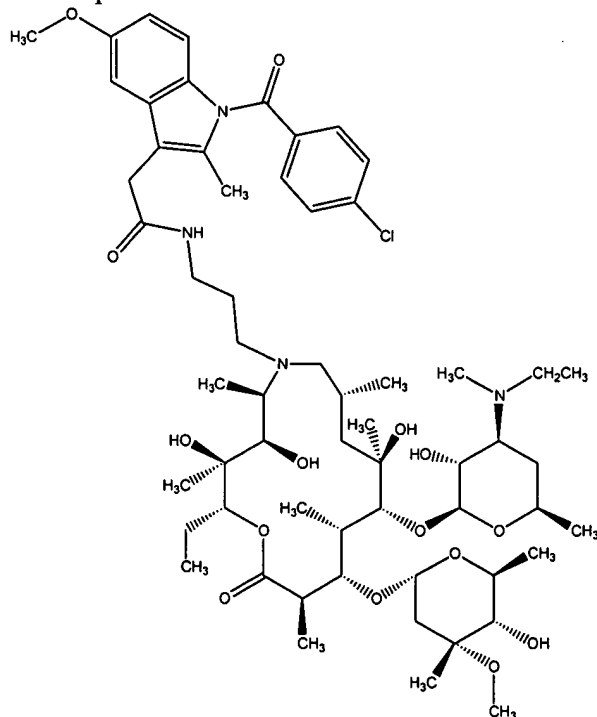
and pharmaceutically acceptable salts and solvates thereof.

20. (Currently Amended) A compound of the formula



and pharmaceutically acceptable salts and solvates thereof.

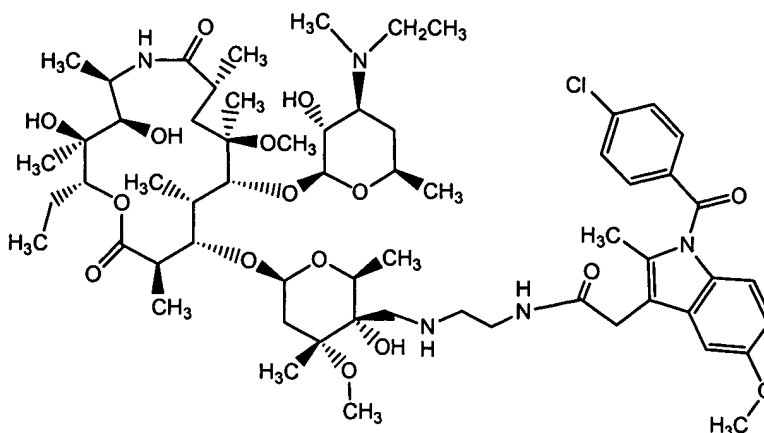
21. (Currently Amended) A compound of the formula



and pharmaceutically acceptable salts and solvates thereof.

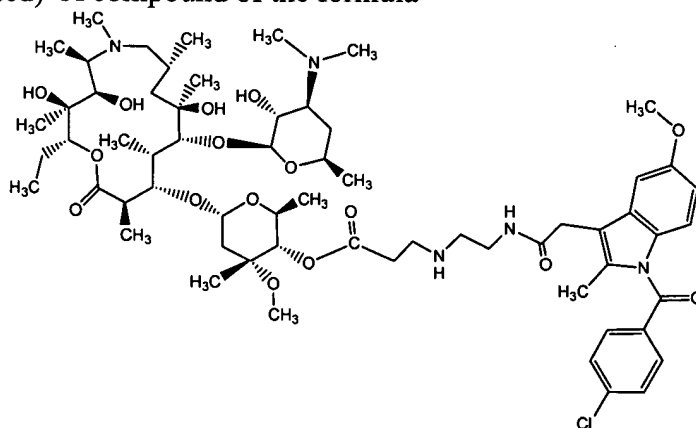
22. (Currently Amended) A compound of the formula





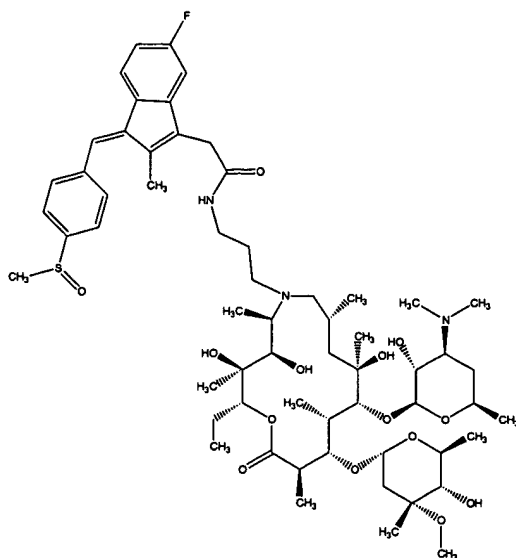
and pharmaceutically acceptable salts and solvates thereof.

23. (Currently Amended) A compound of the formula



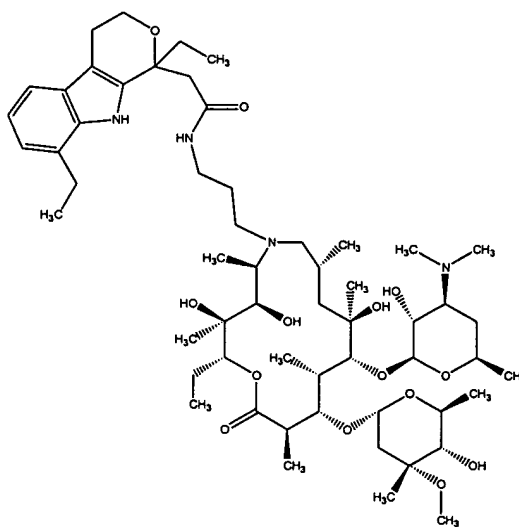
and pharmaceutically acceptable salts and solvates thereof.

24. (Currently Amended) A compound of the formula



and pharmaceutically acceptable salts and solvates thereof.

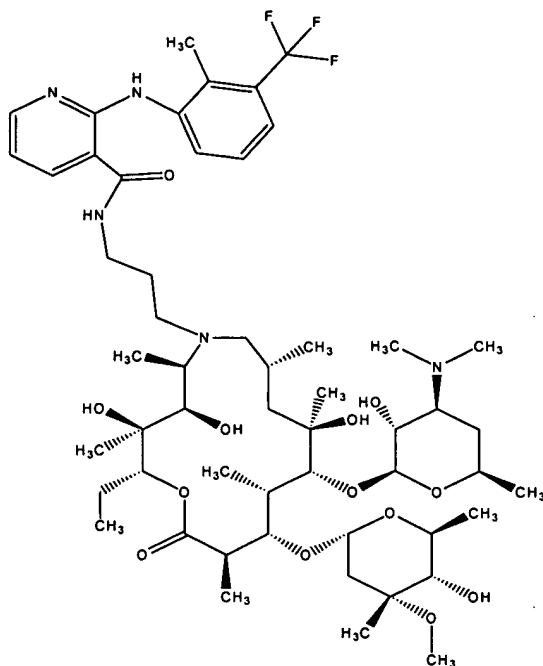
25. (Currently Amended) A compound of the formula



and pharmaceutically acceptable salts and solvates thereof.

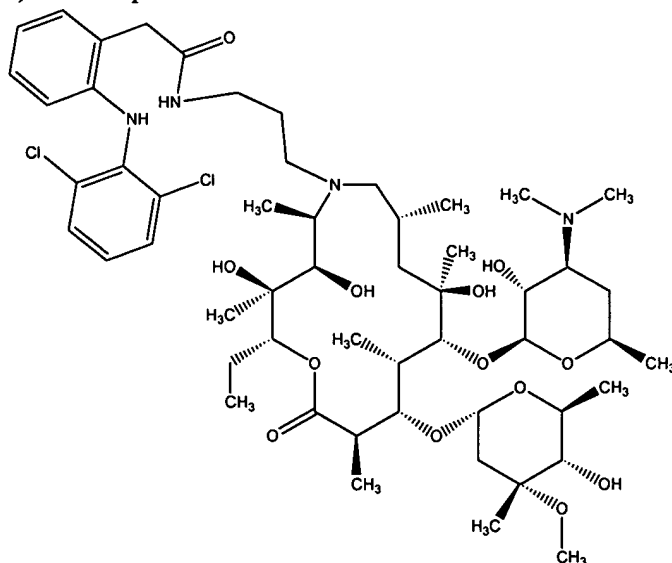
26. (Currently Amended) A compound of the formula





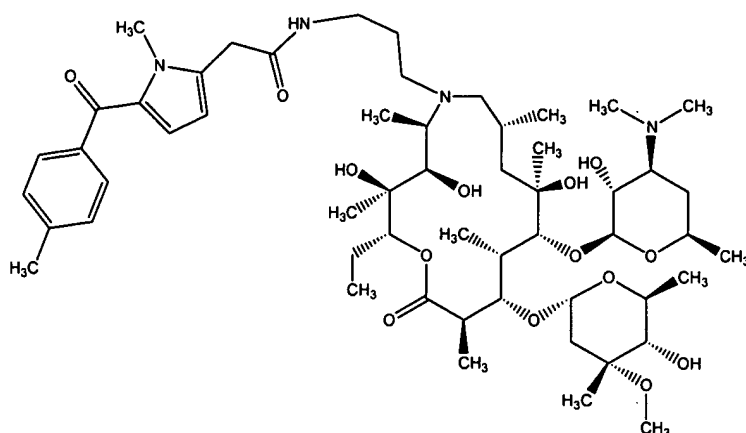
and pharmaceutically acceptable salts and solvates thereof.

29. (Currently Amended) A compound of the formula



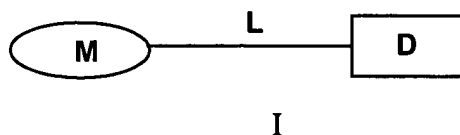
and pharmaceutically acceptable salts and solvates thereof.

30. (Currently Amended) A compound of the formula



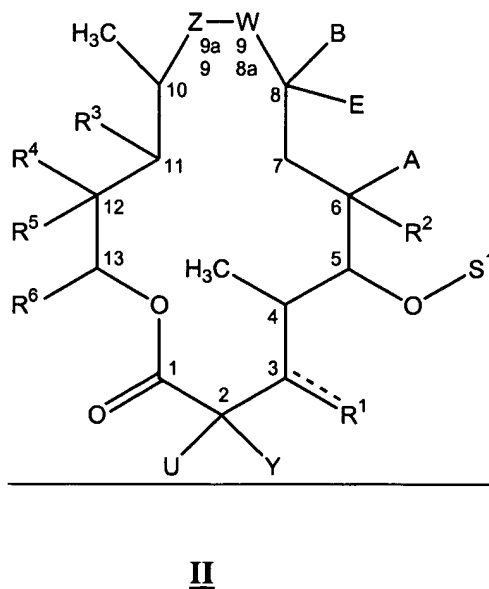
and pharmaceutically acceptable salts and solvates thereof.

31. (Currently Amended) A process ~~Process~~ for the preparation a compound of Formula I

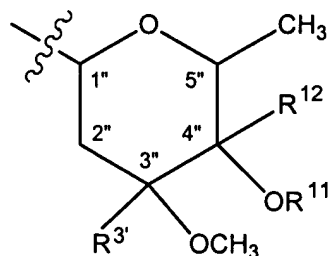


M represents a group of

Formula II:







wherein:

R<sup>3'</sup> is hydrogen or methyl;

R<sup>11</sup> is hydrogen, R<sup>p</sup> or O-R<sup>11</sup> is a group that with R<sup>12</sup> and with C/4'' carbon atom forms a >C=O or epoxy group;

R<sup>12</sup> is hydrogen or a group that with O-R<sup>11</sup> group and with C/4'' carbon atom forms a >C=O or epoxy group;

R<sup>2</sup> is hydrogen, hydroxy, OR<sup>p</sup> or alkoxy

A is hydrogen or methyl;

B is methyl or epoxy;

E is hydrogen or halogen;

R<sup>3</sup> is hydroxy, OR<sup>p</sup>, alkoxy or R<sup>3</sup> is a group that with R<sup>5</sup> and with C/11 and C/12 carbon atoms forms a cyclic carbonate or carbamate; or if W or Z is >N-R<sub>N</sub> R<sup>3</sup> is a group that with W or Z forms a cyclic carbamate;

R<sup>4</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>5</sup> is hydrogen, hydroxy, OR<sup>p</sup>, C<sub>1</sub>-C<sub>4</sub>-alkoxy, or a group that with R<sup>3</sup> and with C/11 and C/12 carbon atoms forms a cyclic carbonate or carbamate;

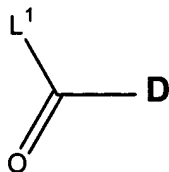
R<sup>6</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl;

wherein M has a linkage site through which it is linked to D via linking group L; provided that the linkage site being at one or more of the following:

- a) any reactive hydroxy, nitrogen, or epoxy group located on S<sup>1</sup>, S<sup>2</sup>, or an aglycone oxygen if S<sup>1</sup> or/and S<sup>2</sup> is cleaved off;
- b) a reactive >N-R<sub>N</sub> or -NR<sub>t</sub>R<sub>s</sub> or =O group located on Z or W;
- c) a reactive hydroxy group located at any one of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>5</sup>;

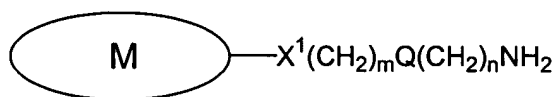






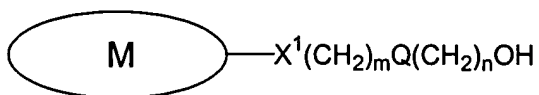
V

wherein L<sup>1</sup> represents a leaving group, and a free amino group of a macrolide represented by Formula **VIa**:



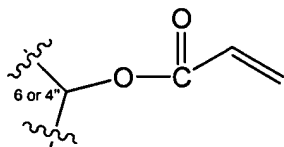
### Vla

b) for a compound of Formula I, where X<sup>2</sup> is -OC(O)-, by reacting a compound of Formula V and the free hydroxyl group of a macrolide represented by Formula VIb:

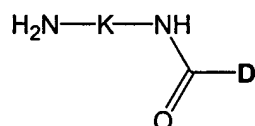


## VIIb

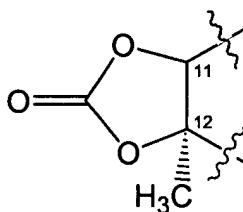
c) for a compound of Formula I, wherein X<sup>1</sup> is -OC(O)-, Q is -NH- and X<sup>2</sup> is -NHC(O)-, by reacting a macrolide represented by formula:



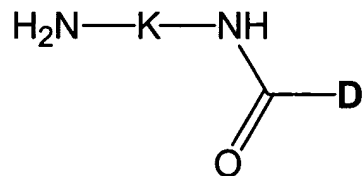
and a free amino group of the compound represented by formula :



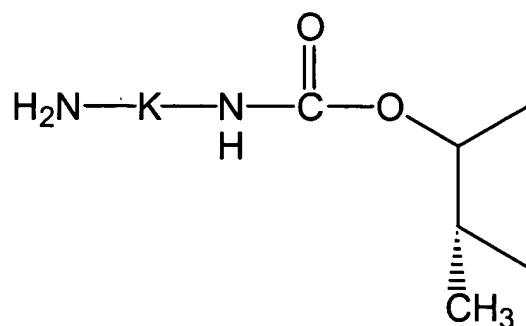
d) for a compound of Formula I, where X<sup>1</sup> is -OC(O)NH- and X<sup>2</sup> is -NHC(O)-, by reacting a macrolide represented by formula



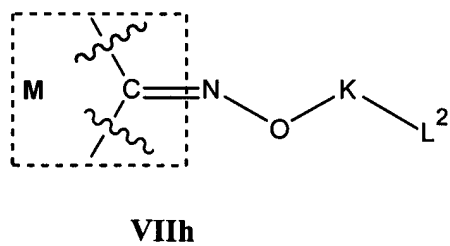
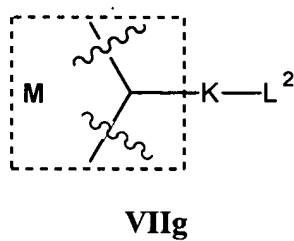
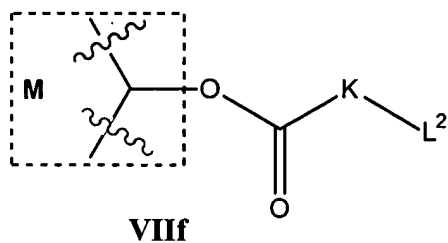
and free amino group of of the compound represented by formula:



e) for a compound of Formula I, where  $X^1$  is  $-CH_2-$ , Q is  $-NH-$  and  $X^2$  is  $-NHC(O)-$ , by reacting a macrolide represented by formula:



f) for a compound of Formula I by reacting a macrolide represented by Formula VIIf or by Formula VIIg or by Formula VIIh having a leaving group L<sup>2</sup>



with a free carboxylic acid of nonsteroidal anti-inflammatory subunit.

32. (Currently Amended) A pharmaceutical composition comprising a compound according to claim 1 ~~and pharmaceutically acceptable salts or solvate solvates thereof~~ as well as a pharmaceutically acceptable diluent or carrier.

33. (Previously Presented) A method of treating inflammatory diseases, disorders and conditions characterized by or associated with an undesirable inflammatory immune response, and all diseases and conditions induced by or associated with an excessive secretion of TNF- $\alpha$  and IL-1 which comprises administering to a subject a therapeutically effective amount of a compound according to claim 1.

34. (Currently Amended) A method of treating inflammatory conditions and immune or anaphylactic disorders associated with infiltration of leukocytes into inflamed tissue in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of ~~the~~ a compound represented by Formula I or a pharmaceutically acceptable salts or solvate thereof according to claim 1.

35. (Previously Presented) The method according to claim 34, wherein inflammatory conditions and immune disorders are selected from the group consisting of asthma, adult respiratory distress syndrome, bronchitis, and cystic fibrosis.

36. (Previously Presented) A method according to claim 34, wherein said inflammatory conditions and immune disorders are selected from the group consisting of inflammatory conditions or immune disorders of the lungs, joints, eyes, bowel, skin, and heart.

37. (Previously Presented) A method according to claim 34, wherein said inflammatory conditions and immune disorders are selected from the group consisting of asthma, adult respiratory distress syndrome, bronchitis, cystic fibrosis, rheumatoid arthritis, rheumatoid spondylitis,

osteoarthritis, gouty arthritis, uveitis, conjunctivitis, inflammatory bowel conditions, Crohn's disease, ulcerative colitis, distal proctitis, psoriasis, eczema, dermatitis, coronary infarct damage, chronic inflammation, endotoxin shock, and smooth muscle proliferation disorders.

38. (Currently Amended) A method for abating inflammation in an affected organ or tissue comprising delivering to said organ or tissue a therapeutically effective amount of ~~the~~ a compound ~~represented by Formula I or a pharmaceutically acceptable salts or solvate thereof~~ according to claim 1.